MEMORANDUM ON POST-VACCINAL ENCEPHALITIS

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The occurrence of post-vaccinal encephalitis proved the subject of fruitful discussion at both the April-May (1) and October (2) meetings of the Paris *Office* in 1946 and several statements on the subject were studied by that body's Permanent Committee. Dr. P. VOLLENWEIDER (3) summarized the complications consequent on primary vaccination in Switzerland since 1940, Dr. C. VAN DEN BERG (4) provided a table showing the number of cases of encephalitis, with deaths, in the Netherlands between 1927 and 1943 and their relation to total vaccinations and revaccinations during that period, and Dr. Melville MACKENZIE (5) gave on account of the occurrence of post-vaccinal encephalitis in England and Wales during the six years of the second world war, together with some observations on the treatment used in certain cases. The author of the present memorandum has summarized these reports in a document (6) which was submitted to the Interim Commission of the World Health Organization. Its contents are recapitulated below:

Dr. VOLLENWEIDER stressed the rarity of the condition in Switzerland since 1940 among children subjected to primary vaccination when between 1 and 3 years of age, but its relative frequency when vaccination was deferred until after the third year. Thus of a total exceeding 800,000 primary vaccinations carried out between 1940 and 1946 the total number of encephalitis cases was: 5 among children from 1 to 3 years of age and 38 among children over 3 years old. Of the 38 cases it was among children between 3 and 8 years of age that the condition most frequently occurred. Moreover there was 1 death from encephalitis among children from 1 to 3 years and there were 11 in those over 3 years. The conclusion reached was that much less risk attends the vaccination of children under 3 years than in older groups.

Dr. VAN DEN BERG's paper was almost entirely statistical.

An analysis of the figures in respect of the Netherlands between 1930 and 1943 is subjoined.

When vaccinated (age-group)	Total number vaccinated	Number of cases of encephalitis	Rate per 10,000 vaccinated	Number of deaths	Rate per 10,000
Under 1 year	298,557	9	0.3	3	0.1
At 1 year	142,737	13	0.9	1	0.07
At 2 years	46,972	6	1.275	1	0.213
At 3 years	31,445	5	1.60	0	0.00
At 4 years	23,823	8	3.36	4	1.70
At 5 years	19,830	4	2.00	1	0.50
6–11 years*	29,382	31	10.50	13	4.40
Over 11 years*	9,323	2	2.15	1	1.075
Total	602,069	78	1.30	24	0.4

* Including revaccinations.

From a discussion on Dr. VAN DEN BERG's statement and on the subject generally at both the April-May and October meetings of the *Office international d'Hygiène publique* Permanent Committee in 1946 the following emerged :

The value of early primary vaccination.

In the Netherlands two scarifications with glycerinated lymph have been used, lymph from many different institutes in many parts of the world having been employed.

Encephalitis could not be considered as resulting from the type of lymph used but from the previous introduction of the casual virus.

There was no relation between occurrence of the complication and the time of year when vaccination was performed.

Race or sex did not appear to influence onset.

The disease, however, seems to occur more frequently in cold, northern countries than in southern countries.

In Roumania there had been no case and in France the complication is extremely rare.

Claims for dried lymph (as prepared at the *Institut vaccinogène de la rue Ballu*, Paris) were advanced by certain French authorities who had failed to observe encephalitis cases following primary vaccination with such lymph among the inhabitants of French colonies.

In the Scandinavian countries, owing to the comparative frequency with which the condition was encountered in earlier years, primary vaccination is limited to children under 2 years of age.

It was considered that primary vaccination should be carried out within the first two years of life and be effected by light scarification,

which does not involve the skin vessels, or by the multiple pressure method.

Dr. Melville MACKENZIE's statement showed that in England and Wales there had occurred during the six years of war 60 cases (31 deaths) of post-vaccinal encephalitis and that in these countries 50 per cent may be taken as the case-fatality rate for this condition, which appears to be a complication of vaccinia, irrespective of the lymph employed. Dr. MACKENZIE also stated that, since 1929, when HORDER in England and, later and independently, HEKMAN in Holland, used blood on serum obtained from a recently vaccinated person, this method of treatment has not infrequently been employed and has sometimes been followed by dramatic recovery; yet recoveries just as dramatic have been seen without it. There was, however, a small balance in favour of the employment of treatment with such blood or serum.

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This memorandum amplifies the information contained in the foregoing documents.

I. HISTORICAL

The occurrence of nervous sequelæ to anti-variolous vaccination was described in the nineteenth century by HEINE (7) in 1860 and by JENDRASSIK and MARIE (8) in 1885. The first case referred to a child of 14 months, the second to one of 9 months. The earliest case in modern literature was portrayed in 1905 by COMBY. In 1912 a further example was provided in England.

II. OCCURRENCE IN THE LAST TWENTY-FIVE YEARS

Not until the 1920's, when outbreaks in England (1922) and the Netherlands (1923-1924) focused medical attention on this unfortunate complication of smallpox prophylaxis, did the condition known as post-vaccinal encephalitis receive recognition as a definite pathological entity.

According to Professor R. JORGE's report on 2 November 1927 to the Smallpox and Vaccination Commission of the League of Nations Health Organization (9), the Netherlands had by then already reported 124 cases and England 82, while sporadic occurrence had been observed in Germany (3 cases in 1927), Austria, Switzerland (2 in 1924), Czechoslovakia (8 in Prague in 1924), Poland (2 in 1927),

France, Portugal (1 in 1922) and the United States (4 in 1927). At the time of the report, however, known cases did not exceed 250 in all.

Precise assessment of the morbidity and mortality arising from post-vaccinal encephalitis throughout the world is impossible; but some idea of the seriousness of this complication may be gauged from the following statistics, incomplete as they are:

III. Incidence and Case-Fatality Rate in Certain Countries. Relation, where possible, of Incidence to the Number of Vaccinations performed, according to Age-Groups

1. *In Europe.*

(a) *In the Netherlands.*

Complete statistics are given in Dr. van den Berg's paper for the period 1930-1943. Dr. Jitta's table, reproduced below, fills in the gap between 1924 and 1926, during which there were 124 cases (1 without relevant details):

Age-group	Number of cases	Number of vaccinations performed each year in each age-group				Proportion of cases to total vaccinations
		1924	1925	1926	Total	
Under 1 year	1	9,989	8,419	8,997	27,405	1 : 27,405
1 year (1 case) 2 years (7) 3 years (34)	42	59,721	58,967	60,570	179,258	1 : 4,268
4 years (27) 5 years (37) 6 years (15)	79	79,936	85,642	87,845	253,423	1 : 3,208
7–12 years	1	11,499	11,072	12,774	35,345	1 : 35,345

By 1928 according to Jitta (10), definitely established cases had risen to 138 out of 197 suspected. Case mortality reached at its maximum 33 per cent. Average incubation period was 11 days (maximum 16, minimum 5 days) after vaccination.

In Jitta's series, incidence in the lower age-groups bore the following proportion to the numbers vaccinated:

Age-group	Proportion	
Under 1 year	1 : 21,000	vaccinations
1–2 years	1 : 49,000	,,
3 years	1 : 15,000	,,
4 years	1 : 4,200	,,
5 years	1 : 3,200	,,
6 years	1 : 3,100	,,

During 1929, the year of smallpox epidemic, there were vaccinated throughout the Netherlands over 1,500,000 persons. Among those vaccinated or revaccinated, there occurred 82 cases of post-vaccinal encephalitis, 56 after primary vaccination, 26 after revaccination.

So great was the fear of post-vaccinal encephalitis that in 1936 there were 1,500,000 children under 6 years old not vaccinated—only 20 per cent of the school-children at that time were vaccinated.

There are no accurate statistics about vaccination in 1944 and 1945, but in 1944 there were 2 cases of post-vaccinal encephalitis reported.

(b) *In Great Britain.*

The condition first became obtrusive in 1922, when 11 cases developed in London. In 1923 there were 51 cases, mostly in the agricultural districts of England.

Between 1922 and 1928 there were reported 93 cases, of which about 50 per cent were fatal.

Between October 1927 and December 1928 there occurred 65 cases, of which 32 were fatal.

Between September 1933 and October 1934 there were 4 cases (3 deaths) in persons ranging from 4 to 18 years, and all after primary vaccinations (3 with 1 insertion, 1 with 2 insertions).

In 1936/37 there were 8 cases, with 5 deaths ; 4 of the cases were in young infants, 4 in children from 10 to 15 years of age, after primary vaccination.

In 1939 one case in a child 14 weeks old was reported 10 days after vaccination with two insertions. Recovery ensued. (Treatment was with whole blood and serum from individuals successfully vaccinated previously.)

In England, between 1932 and 1939, only 8 cases were reported (5 fatal) to the Ministry of Health, London (11).

In England during 1941 a case in an infant 4 months old occurred after an incubation period of eleven days following vaccination. (Recovery : treatment with sodium pentothal in glucose saline intravenously + 5 oz. (150 cc.) " convalescent " serum from two nurses vaccinated three weeks previously).

In Scotland. — Arising out of Scotland's experience of a virulent smallpox outbreak in 1942, the following particulars are germane to the subject of this memorandum :

(i) *Edinburgh.* — In 1942 the number of cases of post-vaccinal encephalitis in Edinburgh City and district was 23 (12) ; incidence amounted to 20 among those not previously vaccinated (18 between 5 and 16 years, 1 at 2½ years and 1 at 28 years) ; 3 cases occurred among those successfully vaccinated in infancy, at 26, 30 and 51 years of age respectively.

The incubation period in this series was from 3 to 12 days.

The relation of incidence of post-vaccinal encephalitis in Edinburgh City to vaccinations performed was 13 cases among 274,441 vaccinated — *i.e.*, 1 : 21,000.

(ii) *Fife.* — Among 75,326 persons vaccinated in 1942 there occurred 9 cases of post-vaccinal encephalitis between 3 and 17 years (4 fatal).

All 9 followed on primary vaccinations, with incubation periods limited to 10-12 days. (Mention was made of the value of large doses (150-200 cc.) of serum of recently vaccinated individuals (13).)

(iii) *Glasgow.* — Among 500,000 vaccinations carried out, mostly in July 1942, there developed 7 cases of post-vaccinal encephalitis—*i.e.*, 1 : 70,000. Of the cases, 6 were in persons over 5 years of age vaccinated for the first time.

In England and Wales, following the 60 cases of post-vaccinal encephalitis, with 31 deaths, which were reported during the 1939-1945 war, 3 civilian deaths were certified as due to this rare complication of vaccination. (Report of the Ministry of Health, London, for the year ended 31 March 1946.)

These three deaths occurred as follows :

(1) in a child aged 5 months ; symptoms 10 days after primary vaccination ;

(2) in a child aged 4 months ; incubation period 6 days after vaccination ;

(3) in a child aged 5 months ; symptoms on 4th day after vaccination.

(c) *In Germany.*

HAMEL (14) gives the following statistics showing the number of cases of post-vaccinal encephalitis, after primary vaccination and revaccination in 1927, 1928 and 1929 (the figures in parentheses

denoting deaths). Primary vaccinations were carried out at 1-2 years of age; revaccinations at 10 years.

Year	Among primary vaccinations	Among revaccinations	Total
1927	13 (7)	3 (3)	16 (10)
1928	20 (6)	1 (1)	21 (7)
1929 (till Oct.) .	13 (4)	1 (1)	14 (5)

Most cases occurred in May-June, in the first two years of life. Incubation period was 11 days mostly.

In 1933 there were 19 cases of post-vaccinal encephalitis, with 3 deaths, of which:

14 cases (1 death) were among primary vaccinations;
5 cases (2 deaths) among revaccinations.

In 1934 (15) there were:

3 cases (1 death) in children of 13 months, 3 years and 12 years; the last-mentioned died.

In 1936 (16) occurred:

5 cases { 1 in a child of 3 months,
1 in a child of 1 year,
3 among children of 3-4 years.

(d) *In Austria.*

In the period 1925-1929, according to KAISER (17), there were reported:

80 cases of post-vaccinal encephalitis, mostly in the Tyrol.

No case was less than 2 years old.

The relation of post-vaccinal encephalitis cases to the number of vaccinations performed in 1927-1929 was:

Year	Proportion Austria	Tyrol
1927	1 : 129,860	1 : 4,570
1928	1 : 17,855	1 : 1,213
1929	1 : 7,749	1 : 641

During 1929 there were 28 cases of post-vaccinal encephalitis in Vienna and Lower Austria (14 in each), with 5 deaths. Most cases occurred in May-June after an incubation period of 9-11 days.

Of the 28: 27 were among primary vaccinations; no case was under 3 years of age. One case, a woman of 22 years, developed among those revaccinated.

As the number of vaccinations performed totalled 175,800, the proportion of post-vaccinal encephalitis cases was 1 : 6,250.

In the period 1930-1937 there were 62 cases, with 28 deaths. All 62, except 3, occurred in children of school age—viz., 1 in first year of life, 1 each at 21 and 29 years. There were 35 between 7 and 8 years.

The incubation period was from 5 to 18 days ; 72.48 per cent of occurrence was between the ages of 8 and 14 years. Eight cases followed revaccination.

Although post-vaccinal encephalitis was made notifiable in Upper Austria in 1925, there was no case till 1930. In 1934 there were reported 15 cases ; in 1935, 10 cases ; in 1936, 1 case.

(e) *In Italy.*

In 1928 there was no case ; in 1934 but 1 case.

In 1936-1937 there were 11 cases among 1,104, 520 primary vaccinations (a proportion of 1 : 100,411). Of the 11 cases, 6 occurred among children of 10-13 months, 5 among children of 2-8 years.

There was no case among the 1,205,971 revaccinations performed n 1936-1937.

(f) *In Greece.*

Very rare in Greece, thanks, doubtless, to the fact that the population is systematically vaccinated and revaccinated in accordance with the law which renders primary vaccination compulsory between the second and twelfth months of life and revaccination in the sixth or seventh year of life.

In practice primary vaccination is carried out between the fourth and sixth months and repeated every two months if unsuccessful.

Revaccination is performed at about 7 years of age, on entry into school, and a second revaccination on enrolment for military service.

(g) *In Roumania.*

No case reported up to 1928.

(h) *In Yugoslavia.*

No case between 1919 and 1929, despite intensive vaccination campaigns.

(i) *In U.S.S.R.*

No case reported up to 1928, although an average of 8-9 million vaccinations carried out annually.

(j) *In France.*

Condition extremely rare; enquiry made in February 1929 (18) secured negative replies from 86 of the 90 Departments, and uncovered only 2 cases among the remaining 4.

No case had been discovered in the Paris area among the 1,324,082 vaccinations performed in the previous six years.

No incidence for France quoted in the general review made by the *Office international d'Hygiène publique* in the proceedings of its Permanent Committee's October session, 1937 (16).

In 1938 there were 2 fatal cases at Marseilles (19):

1 in an infant of 4 months old,

1 in a child of 8 years.

Both were primary vaccinations; incubation periods were 13 and 15 days.

On 4 September 1947, during the fourth session of the Interim Commission, Dr. CAVAILLON informed the Committee on Technical Questions that 10 cases of post-vaccinal encephalitis had recently occurred in France, with 8 deaths, following intensification of vaccination undertaken on account of an epidemic outbreak of smallpox in Paris.

In the Departments of Vienne and Savoie, the grouping of deaths according to age shows that in Vienne deaths occurred on the eighth day after vaccination in children between 5 and 16 months old and in Savoie on the tenth day following vaccination in children aged between 2 and 9 months. In reply to a question by Dr. MORGAN, Dr. CAVAILLON stated that glycerinated lymph was used for these vaccinations.

(k) *In Belgium.*

In the period 1932-1936 (20), there were 11 cases (5 fatal)—*i.e.*, 1 : 150,000.

(l) *In Sweden.*

In the period 1924-1936 there were 53 cases, with 10 deaths (21):

42 cases (8 deaths) after primary vaccination,

11 cases (2 deaths) after revaccination.

The following table shows distribution by age-groups of 42 cases after primary vaccination :

Age-group (in years)	Number of cases	Number of deaths
0– 1	0	0
1– 2	6	1
2– 3	7	0
3– 4	2	0
4– 5	1	0
5– 6	6	2
6– 7	6	2
7– 8	10	3
8– 9	1	0
9–10	3	0

Incidence—22 cases (7 deaths)—heaviest between 5 and 8 years ; only 1 death between 1 and 5 years.

In relation to the number of vaccinations performed, cases of post-vaccinal encephalitis between 1924 and 1928 were, according to KLING, LOENBERG & WASSEN (22) 20 (5 fatal) among 422,827 vaccinated ; *i.e.*, 1 : 21,142. In this series the incubation period was 5-14 days, and the age of incidence from 13 months to 20 years [1].

(m) *In Norway.*

The first case of post-vaccinal encephalitis was observed in 1921. From then until 1937 there were 80 cases, with 39 deaths. In 1937 there were 7 cases (3 deaths) out of 21,908 vaccinations. These 7 cases were mostly in children of 3-7 years, occurring after 10-12 days' incubation period.

The variation in the number of cases to the number of vaccinations is well shown in the following table, which compares Norway and Sweden in this respect :

Year	Proportion per vaccinated in Sweden	Norway
1934	1 : 55,500	1 : 2,770
1936	1 : 18,300	1 : 20,500
1937	—	1 : 3,130

(n) *In Finland.*

On 1 January 1937, the new vaccination law came into effect in Finland making vaccination compulsory for all children before the end of the calendar year in which they attained the age of 2 years. Children not vaccinated before this age limit had still, with certain exceptions, to be vaccinated.

[1] See note by N. O. HEINERTZ, p. 58.

In 1937 out of 162,000 vaccinated (56 per cent of those due), there were 5 cases of post-vaccinal encephalitis (1 death)—*i.e.*, a proportion of 1 case per 32,400 children vaccinated.

(o) *In Denmark.*

Up to 1940 (23) there had been 12 cases of post-vaccinal encephalitis (6 fatal). All 6 fatal cases were between 6 and 7 years of age. All 12 cases followed primary vaccinations.

2. *In Africa.*

(a) *Angola.*

Although many thousands of vaccinations had been performed annually in Angola, the first recorded case of post-vaccinal encephalitis was in 1928, in a mulatto child of 4½ months. Recovery. There is no record of further occurrence.

(b) *Belgian Congo.*

No case had been reported between 1929 and 1934 during which period 1,800,000 primary vaccinations had been carried out. There is no record of occurrence since that time.

(c) *Kenya.*

In 1940 (24) there were reported 6 cases, with 3 deaths, all between 2¼ and 54 years.

(d) *Uganda.*

In 1947 (25), two probable cases among African children have been reported. Previous to that year only one case had been recorded out of millions of vaccinations performed.

(e) *Morocco.*

No case so far reported.

(f) *Egypt.*

Only very few cases of post-vaccinal encephalitis have been recorded in Egypt, probably because the law requires all children to be vaccinated within the first three months of life.

3. *In America.*

(a) *In the United States.*

According to ROSENAU (26) there is record of 38 probable cases of post-vaccinal encephalitis in the United States during seven years (unspecified), 10 of which occurred in 1927 and 13 in 1930.

In 1933 there were reported 5 cases among primary vaccinations in children of from 3 to 9 years.

(b) *In Mexico.*

Between 1928 and 1935 (27) there were 8 cases, 4 deaths. Of these 8 cases, all occurred after primary vaccinations, 7 in the first year of life, 1 at 5 years.

(c) *In Uruguay.*

Between 1927 and 1940 (28) there developed, at Montevideo, after primary vaccination, and after incubation periods of 8-13 days, 13 cases of post-vaccinal encephalitis, with 7 deaths.

The ages of incidence were : 1 at 3 months ; 9 between 3 and 7 years, 1 at 8 years, 1 at 10 years (1 unrecorded).

The proportion of cases to the numbers vaccinated were :

In 1933	1 : 2,651	
In 1935	1 : 5,163	
In 1936	1 : 94,170	(in a smallpox year)
In 1939	1 : 4,933	

(d) *In British Guiana.*

According to GRACE (29), there occurred in 1928 one case in a girl aged 15 years, after an incubation period of 11 days, with death 4 days later.

This case was stated to have been the only one reported in the Tropics up till 1928.

4. *In Asia.*

In India.

In 1938 (30) there developed 1 case in the Punjab at Murree in a Hindu baby of 11 months, after an incubation period of 11 days.

5. *In Oceania.*

In Australia.

According to SWAN (31), one fatal case—the only one so far reported—occurred in a soldier of 47 years.

IV. ÆTIOLOGY

Two main views are held :

(a) The condition is due to an unknown virus X, which is activated by the vaccinia—*i.e.*, it is comparable with herpes which appears to be present always in the body, but is quiescent until another disease has prepared the ground.

(b) It is part of vaccinia comparable with nephritis complicating scarlet fever. In this connexion, however, the finding of vaccine virus in the brain and spinal cord has, in the case of post-vaccinal encephalitis, no causative significance, as the vaccine virus is widely disseminated through the nerve tissues in the course of ordinary vaccination.

Other views which may be cited are :

(c) That toxins from a tonsillar or pulmonary infection can give rise to a non-specific perivascular encephalitis ; thus a vaccine virus may affect the reticulo-endothelial system or the brain itself in such a way that the provocation of an encephalitis by certain toxins is facilitated (HEERUP).

(d) That there is no need to assume that there is a second virus as the cause. It seems there must be some special predisposition (personal, familial or regional) which causes their development (LUCKSCH).

Today the bias of opinion is in harmony with that expressed by the Commission on Smallpox and Vaccination, Health Organization, League of Nations, in August, 1928 (32) :

> " It would appear, in our present state of knowledge, that the virus of vaccinia of itself cannot be considered responsible for the supervention of encephalitis. Rather it has to be supposed that some unknown factor exists—perhaps bacterial or a filter-passing virus, or a latent virus—which, by means of a reciprocal reaction, determines the occurrence of the accidents in question."

Experimental work carried out by KELLER & SCHAEFFER (33) suggests at most activation of a hitherto unknown virus or of a non-pathogenic agent, which has become pathogenic as a result of vaccinial allergy.

V. HISTOPATHOLOGY

The histopathological changes produced by this condition are those seen in encephalitis following smallpox, chickenpox, measles and certain other naturally acquired diseases—viz., perivascular demyelination, accompanied by destruction of the axis cylinders of the medullary sheaths, together with extra-adventitial and perivascular infiltration with polymorphic microglial cells and granular corpuscles.

VI. Prophylaxis

There are no certain means of avoiding post-vaccinal encephalitis. Various prophylactic measures suggested, however, include :

(a) the performance of primary vaccination during the first two months of life ;

(b) the use of vaccine which is not too potent (dilution of vaccine) ;

(c) vaccination by one or at most two scarifications ;

(d) employment of subcutaneous and intracutaneous vaccination ;

(e) for older children or adults who have not been previously vaccinated, a dose of vaccinial immune serum to be given at the same time as the vaccine.

Paschen (34) observes, however, that the recommendation of Rolleston to use only one insertion is but a counsel of despair, as the complication has occurred after the slightest as well as the severest reaction and even after intracutaneous vaccination.

VII. Treatment

The following methods of treatment have been recommended :

(a) The use of whole blood or serum from a recently vaccinated person (belonging to the same blood group) in a dosage sufficiently large and administered sufficiently early to provide the patients with an effective amount of neutralizing antibody. (Examples : large doses (150-200 cc.) of serum of recently vaccinated individuals were usefully employed in Fife, Scotland, in 1942 ; also the combination of whole blood and serum from previously vaccinated persons.)

(b) The use of sodium pentothal (0.025 gm.) with glucose saline administered intravenously, together with 5 oz. (150 cc.) serum of recently vaccinated persons.

(c) The use of sulphapyridine, sulphathiazole or sulphadiazine with or without serum.

The real value of treatment is difficult to assess, as the condition so often clears up spontaneously.

VIII. Remarks

(i) It is generally accepted that, based on the experience of the Netherlands and England, post-vaccinal encephalitis occurs

more rarely in infants under the age of 2 years than in older children and in adults.

Thus from the figures provided in this paper there were in the Netherlands (1924-1926) 123 cases, of which only 1 (0.813 per cent) occurred under 2 years, 122 (99.187 per cent.) between 2 and 12 years ; there were 98.3 per cent. between 3 and 6 years.

So in Austria (1930-1937) : of 59 cases among children of school age, 35 (60 per cent) were between 7 and 8 years. In this series there was no case under 3 years.

In Sweden (1924-1936) : of the 42 cases recorded, 6 (12.5 per cent) were under 2 years ; 36 (66.6 per cent) were between 2 and 8 years.

In Germany, on the other hand (1927-1929) there were 46 cases mostly under 2 years. In Italy also (1936-1937) : of the total 11 cases, 6 (54-55 per cent) were under 2 years and 5 (45.45 per cent) were between 2 and 8 years.

(ii) The earliest ages at which post-vaccinal encephalitis has been reported have been, according to this paper's statistics, 3 months (Germany and Uruguay), 3½ months (England), 4 months (England and France), 4½ months (Angola), 5 months (England).

(iii) The incubation period—*i.e.*, the period elapsing between vaccination and the onset of symptoms of encephalitis—is ordinarily 10 to 12 days, 11 days being commonest. In this paper incubation periods, however, of 3 days (Scotland), 4 days (England) 5 days (Austria and Sweden) and 6 days (England) have been recorded. Elsewhere incubation periods of 2 days (England) as minimum and of 32 days (England) as maximum have been chronicled.

(iv) The ratio of incidence to the number of vaccinations performed varies widely and is related to age-group, year and locality. Thus in JITTA's series for the Netherlands (1924-1926) the over-all proportion was 124 cases to 495,431 vaccinations—*i.e.*, 1 : 4,000 ; but for children under 1 year the proportion was 1 : 27,405, for children from 1 to 3 years it was 1 : 4,268, for those between 4 and 6 years it was 1 : 3,208 and for those between 7 and 12 years it was 1: 35,345. Again, whereas the proportion in 1927 was 1 : 129,860 in Austria and 1 : 4,570 in the Tyrol, it was in 1929 in Austria 1 : 7,749 and in the Tyrol 1 : 641.

(v) No single method of carrying out vaccination has been exclusively concerned with the occurrence of post-vaccinal encepha-

litis, nor would there seem to be any association between the incidence of this complication and the type of vaccine lymph employed.

(vi) Geographical distribution throughout the world has been uneven, as also it has been within countries themselves. The preponderance of incidence in Western-European countries is evidenced by this paper's statistics ; and in these countries the inequality of attack is amply illustrated by the disproportionate incidence between Austria as a whole and the Tyrol (1925-1929 : 80 cases in Austria, mostly in the Tyrol), between the Netherlands as a whole and certain of its communes (1924-1927 : 139 cases in all the Netherlands out of a population of 7,526,000—*i.e.*, 1 : 54,148 ; and 62 cases among communes with less than 5,000 inhabitants but with a combined population of 1,868,930—*i.e.*, 1 : 30,144 inhabitants) and between Sweden as a whole and its southern territory (1926-1936 : 67 cases, 10 deaths, in Sweden, mostly in the southern part of the country).

(vii) Diverse views are held on the ætiology of post-vaccinal encephalitis, but a majority of opinion favours the explanation that the condition is due to the presence of an unknown virus, previously introduced into the body, but remaining quiescent until activated by the vaccinia.

(viii) The histopathological changes brought about by this complication are those met with in encephalitis following smallpox, chickenpox, influenza, measles and certain other naturally acquired diseases.

(ix) While there are no certain means of avoiding post-vaccinal encephalitis, various prophylactic measures have been advocated, the most important of which is the performance of primary vaccination during the first two months of life.

(x) The real value of treatment is difficult to assess, as the condition so often clears up spontaneously. Methods of treatment include the use of *(a)* whole blood or serum from a recently vaccinated person of the same blood group in a dosage sufficiently large to provide the patient with an effective amount of neutralizing antibody ; *(b)* sodium pentothal (0.025 gm.) in glucose saline intravenously plus " immune " serum as in *(a)* ; *(c)* sulphapyridine, sulphathiazole or sulphadiazine, with or without serum.

(xi) Incidence of and mortality from post-vaccinal encephalitis occur much less frequently in children under 2 years of age than in older children and adults.

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